CF MOUSE SURVIVAL IS IMPROVED BY LENTIVIRAL CFTR AIRWAY GENE TRANSFER

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Introduction

We have shown that long term (> 12 month) partial CFTR c… be achieved in… CF … treated with a lentiviral (LV) vector. In this gene transfer study a repeated-measures study … used to extend our ability … the effects of CFTR gene correction in individual CF mice.

Methods

Male and female CF mice (cftr^{tm1Unc}) were … Control animals were pre-treated with … (LPC, 0.3%, 4 µl) prior to a lentiviral (… vector that contained no gene (LV-MT, n=6), or with a saline (PBS, 4 µl) … CFTR, n=6). The primary treatment group received LPC prior to LV-CFTR (n=12). Viral titre was … CFTR function was assessed by nasal … (PD) measurement at 1 week, 1 and 3 months, and then at 3 … intervals. Mouse group survival was expressed as Kaplan-Meier plots, with survival differences determined by Mantel–Cox log rank test. Outcomes were also compared to survival data from Luciferase (Luc) reporter gene studies in 2 groups of normal C57 mice …

Results

1) Significant and persistent functional CFTR gene transfer ($p<0.05$, ANOVA) was present in the nasal airway for up to 12 months (ΔPD_{CL} range 12-54% towards normal) in CF mice treated with LPC/LV-CFTR (Fig.1).
2) In the two control groups the mean ΔPD … LV-MT treatment was no different to that in … CF mice.
3) LPC/CFTR significantly extended median survival (20.1 mo), compared to either PBS/LV-CFTR (14.4 mo) and LPC/LV-MT (8.8 mo) control groups (Fig. 2).
4) Survival in normal C… mice sim… gene Luc was no different between all groups with a median survival greater than 23 months (Fig. 3).
5) Historical C57BL/6 strain data (JAX Laboratories, USA) showed that survival of tw… CFTR … CF mice was not significantly different from normal untreated C57 mice.

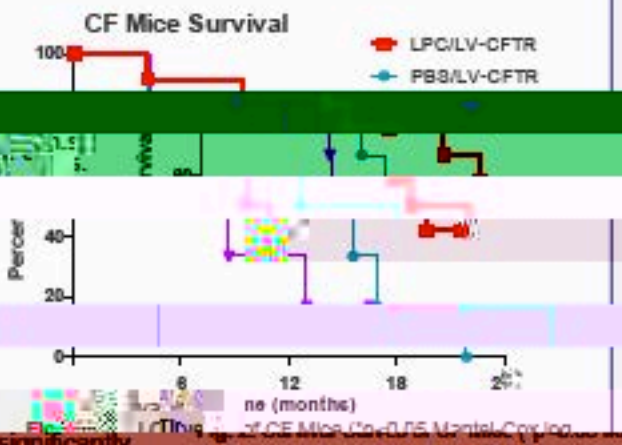

Fig. 2. … of CF Mice (p<0.05 Mantel-Cox log rank test, n=6-12)

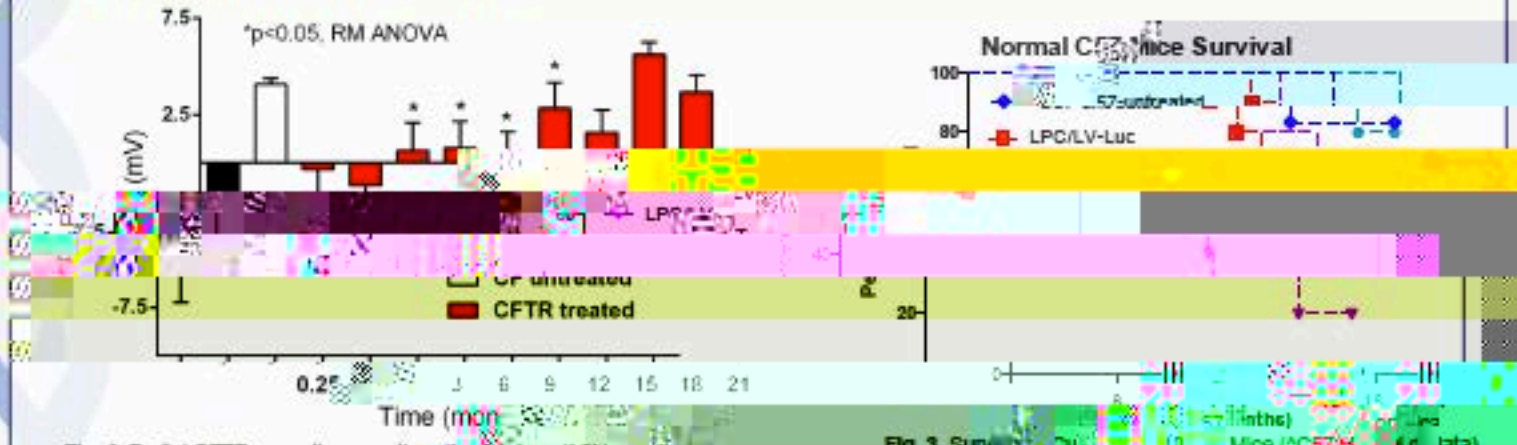

Fig. 1. Partial CFTR correction over ti… ANOVA, n=3-12).

Fig. 3. … Mice (…C57 Historical Data).

Conclusion

These … significantly improve lifetimes of treated animals. Some nasal dose could reach lung airways … via "spillover" of gene vector … potentially improve CFTR function there, with … indirect benefits. Further studies … essential to determine the … for the substantial improvement in animal survival follow… such limited airway gene transfer

Ackn… eager…

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